REMARKS

STATUS OF THE CLAIMS

Claims 1-4, 6-11, 14, 17-19 and 21-33 were pending. Claim 1 has been amended to eliminate the negative proviso and Claim 21 has been amended to depend from claim 1. Claims 10 and 31 have been amended to indicate that at least one of the zinc fingers is a C_3H zinc finger, as described, for example, on page 10, line 30. Thus, claims 1-4, 6-11, 14, 17-19 and 21-33 are pending as shown above.

In light of the fact that the foregoing amendments obviate all the remaining rejections, thereby simplifying the issues in this case and eliminating the need for appeal, entry after final is requested.

RESTRICTION REQUIREMENT

Applicants' traversal of the Restriction Requirement has been deemed unpersuasive on the grounds that "a proper search of the pending claims does require a separate search for each functional domain." (Final Office Action, page 2).

Applicants again traverse. Claims 14 and 33 require that the functional domain be present with the zinc finger protein of claim 1. Therefore, with regard to any alleged separate search, it remains the case that a search of the art for the zinc finger proteins (or polynucleotides encoding these zinc finger proteins) of claim 1 would necessarily and inevitably reveal **all** references relevant (under 35 U.S.C. §§ 102, 103 or 112) to claims 14 and 33. Thus, Restriction as between the members of the claimed Markush groups remains improper.

The Examiner also alleges that the members of the Markush group are not related because they "do not share substantial structural features essential to a common utility." *Id.* However, in the rejection under 35 U.S.C. § 102, the Examiner states that all zinc finger proteins have the "same chemical composition, *i.e.*, they are composed of amino acids." *Id.* In other words, the Examiner defines the common structure of zinc finger proteins to be their amino acid composition. Accordingly, the members of the claimed Markush group share a common structural feature as defined by the Examiner (*i.e.*, they are all composed of amino acids), which common structure is related to their utility as transcriptional regulators. Therefore, according to

the criteria established by the Examiner, the members of the Markush group are clearly related. Thus, the Restriction is improper and should be withdrawn.

35 U.S.C. § 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION (NEW MATTER)

Claims 1-4, 6-11, 14, and 17-19 were rejected as allegedly not described in the specification in such a way as to reasonably convey to the skilled artisan that applicants were in possession of the claimed subject matter. (Final Office Action, page 3). This rejection was based on the assertion that the limitation "between about 5 and 50 amino acids in the backbone region of each zinc finger and wherein the backbone region is not derived from zif268 of TFIIIA" is not supported by the as-filed specification. *Id.*

It is well settled that the proscription against the introduction of new matter in a patent application (35 U.S.C. 132 and 251) serves to prevent an applicant from adding information that goes beyond the subject matter originally filed. *See, e.g., In re Rasmussen*, 650 F.2d 1212, 1214, 211 USPQ 323, 326 (CCPA 1981) and MPEP § 2163.06. Literal description is not required (M.P.E.P. § 2163.02):

> The subject matter of the claim need not be described literally (i.e., using the same terms or in haec verba) in order for the disclosure to satisfy the description requirement.

Thus, the written description requirement is satisfied if the specification reasonably conveys possession of the invention to one skilled in the art. *See, e.g., In re Lukach*, 169 USPQ 795, 796 (CCPA 1971). The disclosure must be read in light of the knowledge possessed by the skilled artisan at the time of filing, for example as established by reference to patents and publications available to the public prior to the filing date of the application. *See, e.g., In re Lange*, 209 USPQ 288 (CCPA 1981). Moreover, the burden is on the Examiner to provide evidence as to why a skilled artisan would not have recognized that the applicant was in possession of claimed invention at the time of filing. *Vas Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111 (Fed. Cir. 1991); *In re Wertheim*, 191 USPQ 90 (CCPA 1976).

Here, the as-filed specification clearly conveys that Applicants were in possession, at the time of filing, of zinc finger proteins whose backbones are not derived from Zif268 or TFIIIA and having between about 5 and 50 amino acids between the zinc fingers:

> A zinc finger "backbone" is the portion of a zinc finger outside the region involved in DNA major groove interactions; *i.e.*, the regions of the zinc finger outside of residues –1 through +6 of the alpha helix. The backbone comprises the beta strands, the connecting region between the second beta strand and the alpha helix, the portion of the alpha helix distal to the first conserved histidine residue, and the inter-finger linker sequence(s). Thus, a plant zinc finger "backbone" refers to sequences derived from one or more plant ZFPs, where these sequences are not naturally involved in DNA major groove interactions.[1]
>
> Currently, ZFPs targeted to specific predetermined sequences are derived from non-plant ZFPs such as Xenopus TFIIIA, murine zif268, human SP-1 and the like. Accordingly, in one embodiment, modified plant zinc finger proteins, targeted to predetermined sequences, are described wherein all or substantially all of the sequences making up the ZFP are derived from one or more plant sources.[2]
>
> In contrast to typical non-plant ZFPs, plant ZFPs are characterized by long spacers between adjacent fingers. Thus, in certain embodiments, a non-plant structure refers to ZFPs which contain tandem arrays of zinc fingers, i.e., structures in which there are between 5 and 50 amino acids between fingers, more preferably between 5 and 25 amino acids and even more preferably between 5 and 20 amino acids, or any integer therebetween.[3]
>
> In certain embodiments, one or more amino acid residues are deleted between one or more of the zinc fingers.[4]

Accordingly, no new matter was added by the amendments made in the paper filed February 27, 2006.

Moreover, the presently pending claims do not contain the recitation that the backbone region is not derived from *zif268* or TFIIIA.

For all of the aforementioned reasons, the rejection should be withdrawn.

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[1] Page 10, lines 10-16 of the as-filed specification
[2] Page 7, lines 1-2 of the as-filed specification
[3] Page 18, line 29 to page 19, line 3 of the as-filed specification
[4] Page 4, lines 22-23 of the as-filed specification; original claims 12 and 13

35 U.S.C. 112, FIRST PARAGRAPH, ENABLEMENT

Claims 10 and 31 were again rejected under 35 U.S.C. § 112, 1st paragraph as allegedly not enabled by the specification as filed. In particular, it was asserted that the specification does not teach one of skill in the art how to make or use "non-canonical" zinc finger proteins (Final Office Action, paragraph bridging pages 4-5):

> The Examiner maintains that the full scope of the claimed invention is not enabled. The outstanding rejection is not predicated on the failure of the specification to disclose or define non-canonical zinc finger proteins. The outstanding rejection was predicated on the failure of the specification to provide guidance with respect to how to alter the structure of the zinc finger backbone of a non-canonical zinc finger standard. In this regard the Examiner maintains that the skilled artisan would not know how to make and use non-canonical fingers so as to retain their binding functionality, ...

Pending claims 10 and 31 are drawn to zinc finger proteins in which at least one zinc finger is a C_3H zinc finger. Because the as-filed specification clearly enables the skilled artisan to make and use zinc finger proteins that include C_3H zinc fingers, Applicants traverse the rejection.

As a threshold matter, Applicants note that the term "non-canonical zinc finger protein" is defined beginning at page 10, line 25 of the specification as one that differs from the canonical Cys2-His2 structure. Included within this definition (page 10, lines 29-30) are the Cys3-His proteins now recited in claims 10 and 31.

Nonetheless, Applicants reiterate that the canonical or non-canonical nature of the zinc coordinating residues does not in any way change how the backbone and/or recognition helices of any naturally occurring plant zinc finger can be altered according to the teachings of the specification. Simply put, the canonical or non-canonical nature of the particular zinc finger will not change when residues in the recognition region are altered or when residues in the interfinger region are deleted. Given that zinc coordinating residues need not be altered, the skilled artisan would recognize that alterations to any non-canonical C_3H zinc finger in the remainder of the backbone, *e.g.*, to shorten the inter-finger regions, would not affect binding functionality of either non-canonical or canonical zinc fingers. Therefore, basis of the rejection is unfounded and the rejection should be withdrawn.

Turning to the canonical and non-canonical fingers *per se*, Applicants submit that, as pointed out above, the specification as filed clearly defines canonical and non-canonical zinc fingers (*see, e.g.,* page 10, line 25 to page 11, line 2) and, moreover, establishes that C_3H zinc fingers as set forth in claims 10 and 31 were well known to those of skill in the art at the time of filing (*see,* page 2, lines 17-19):

> Another class of ZFPs includes the so-called C_3H ZFPs. See, *e.g.,* Jiang *et al.* (1996) *J. Biol. Chem.* 271:10723-10730 for a discussion of Cys-Cys-His-Cys (C_3H) ZFPs.

The specification also teaches how to identify the zinc coordinating residues of any protein and, as such, identify canonical or non-canonical zinc fingers. (*See, e.g.,* Example 1). Therefore, at of the time of filing, it was well known that C_3H non-canonical zinc fingers would coordinate zinc and bind to DNA.

Accordingly, claims 10 and 31 as pending are fully enabled by the as-filed specification and withdrawal of the rejection is in order.

35 U.S.C. § 102/103

Claims 1-4, 6-9, 11, 17-19, 21-30 and 32 were rejected as allegedly anticipated or obvious over U.S. Patent No. 6,140,466 (hereinafter "Barbas"). (Final Office Action, pages 6-8). It was alleged that the claimed zinc finger proteins are not distinguished from Barbas on the grounds that the proteins will have the "same chemical composition, *i.e.*, they are composed of amino acids." *Id.*

As a threshold matter, Applicants note that the test for determining identity of proteins as set forth in the Final Office Action is improper. The Final Office Action asserts that, regardless of their sequence, all proteins have the "same chemical composition" because they are all made up of amino acid residues. *Id.* However, the Patent Office has consistently indicated that protein structure (and function) depends on the particular amino acid sequence of the protein. In other

words, in order to anticipate a claimed protein, the protein of the reference must have the same amino acid sequence as the claimed protein.[5]

In the case at hand, as repeatedly noted, Barbas's ZFPs are derived from one of two animal ZFPs, *i.e.,* Zif268 (mouse) or TFIIIA (frog). By contrast, the claimed ZFPs are derived from a plant ZFP. Furthermore, in making his ZFPs, Barbas alters only the 7 amino acids located in the recognition helix of the zinc finger. In other words, any difference(s) between Barbas's proteins and wild-type Zif268 or TFIIIA is (are) only in the recognition helix; thus all of Barbas' ZFPs retain either a Zif268 or a TFIIIA backbone sequence. Consequently, in order to show that Barbas anticipates the claimed methods (which use ZFPs comprising modified plant ZFP backbones), the Office must demonstrate that zinc finger proteins derived from plant ZFPs, by deletion of inter-finger residues, have the backbone amino acid sequence of wild-type Zif268 or TFIIIA. This has not been shown and cannot be shown because there is little sequence homology between plant and animal ZFPs outside of the 4 zinc coordinating residues. *See, e.g.,* Englebrecht et al. (Ref. C70 of IDS filed June 9, 2005), Abstract):

> They [plant ZFPs] exhibit remarkable differences in the features of their zinc finger sequences and zinc finger arrangements compared to animal zinc finger proteins.

Furthermore, not only are plant and animal ZFPs structurally different in the inter-finger region, but naturally occurring plant ZFPs also exhibit considerable sequence diversity outside the zinc finger region (*see, e.g.,* Meissner et al. (Reference AH-2 of IDS filed December 27, 2002, Abstract):

> Outside of the zinc finger regions, there is considerable sequence diversity, including the sequence and length of the inter-finger region...

Hence, a ZFP as disclosed in Barbas, that includes only changes to residues in the recognition helix of TFIIIA or Zif268 will never be identical in sequence to a ZFP derived from a plant ZFP, as recited in the claims. This is illustrated by the following sequence alignment, which shows the lack of homology between either of Zif268 and TFIIIA, on the one hand, and

[5] Indeed, if identity as between two proteins was determined as set forth in the Final Office Action, any protein sequence would anticipate another (different) protein sequence because they are both "composed of amino acids."

either (1) naturally occurring plant zinc finger proteins (Englbrecht, Ref. C70 of IDS filed June 9, 2005) or (2) exemplary proteins as claimed, on the other (where the recognition helices are shown as 7 "X" residues, and noting that the amino acids represented by "X" are the only residues that can vary in sequence in Barbas' ZFPs):

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Englbrecht fig.1 At1g68130:   (X20)RTLLESDRYVC--EICNQGFQXXXXXXXHRRRHKVPWKLLK
Barbas Zif268-finger1:               MKLLEPYACPVESCDRRFSXXXXXXXHIRIHT
Zif268-finger2:                        GQKPFQC--RICMRNFSXXXXXXXHIRIHT
Zif268-finger3:                        GEKPFAC--DICGRKFAXXXXXXXHTKIHL
SEQIDNO:17                             KSKGHEC--PICFRVFKXXXXXXXHKRSHTGEKP
SEQIDNO:18                                 YKC--TVCGKSFSXXXXXXXHKRLHTGEKP
SEQIDNO:19                                 FSC--NYCQRKFGXXXXXXXHVRIHQNKK

Englbrecht fig.1At1g68130:    RETNEEVRKRVYVCPEPTCLHHNPCHALGDLVGIKKHFRRKHSNHKQ
Barbas Zif268-finger1:             MKLLEPYACPVESCDRRFSXXXXXXXHIRIHT
Zif268-finger2:                      GQKPFQC--RICMRNFSXXXXXXXHIRIHT
Zif268-finger3:                      GEKPFAC--DICGRKFAXXXXXXXHTKIHL
SEQIDNO:17                           KSKGHEC--PICFRVFKXXXXXXXHKRSHTGEKP
SEQIDNO:18                               YKC--TVCGKSFSXXXXXXXHKRLHTGEKP
SEQIDNO:19                               FSC--NYCQRKFGXXXXXXXHVRIHQNKK

Englbrecht fig. 5 At1g66140:       RVFSCNY--CQRKFYXXXXXXXHQNAHKRERTLAKRX
Barbas Zif268-finger1:           MKLLEPYACPVESCDRRFSXXXXXXXHIRIHT
Zif268-finger2:                    GQKPFQCRI--CMRNFSXXXXXXXHIRIHT
Zif268-finger3:                    GEKPFACDI--CGRKFAXXXXXXXHTKIHL
SEQIDNO:17                         KSKGHEC--PICFRVFKXXXXXXXHKRSHTGEKP
SEQIDNO:18                             YKC--TVCGKSFSXXXXXXXHKRLHTGEKP
SEQIDNO:19                             FSC--NYCQRKFGXXXXXXXHVRIHQNKK

Englbrecht fig.1 At1g68130:   (X20)RTLLESDRYVC--EICNQGFQXXXXXXXHRRR-HKVPWKLLK
Barbas TFIIA-finger1:                      YICSFADCGAAYNXXXXXXXHLCK-HT
TFIIA-finger2:                             FPCKEEGCEKGFTXXXXXXXHSLT-HT
TFIIA-finger3:                             FTCDSDGCDLRFTXXXXXXXHFNRFH
SEQIDNO:17                           KSKGHEC--PICFRVFKXXXXXXXHKRS-HTGEKP
SEQIDNO:18                               YKC--TVCGKSFSXXXXXXXHKRL-HTGEKP
SEQIDNO:19                               FSC--NYCQRKFGXXXXXXXHVRI-HQNKK

Englbrecht fig.1At1g68130:    RETNEEVRKRVYVCPEPTCLHHNPCHALGDLVGIKKHFRRKHSNHKQ
Barbas TFIIA-finger1:                        YICSFADCGAAYNXXXXXXXHLCK-HT
TFIIA-finger2:                               FPCKEEGCEKGFTXXXXXXXHSLT-HT
TFIIA268-finger3:                            FTCDSDGCDLRFTXXXXXXXHFNRFH
SEQIDNO:17                             KSKGHEC--PICFRVFKXXXXXXXHKRS-HTGEKP
SEQIDNO:18                               YKC--TVCGKSFSXXXXXXXHKRL-HTGEKP
SEQIDNO:19                               FSC--NYCQRKFGXXXXXXXHVRI-HQNKK


Englbrecht fig. 5 At1g66140:       RVFSCNY--CQRKFYXXXXXXXHQNA-HKRERTLAKRX
Barbas TFIIA-finger1:                YICSFADCGAAYNXXXXXXXHLCK-HT
TFIIA-finger2:                       FPCKEEGCEKGFTXXXXXXXHSLT-HT
TFIIA-finger3:                       FTCDSDGCDLRFTXXXXXXXHFNRFH
SEQIDNO:17                         KSKGHEC--PICFRVFKXXXXXXXHKRS-HTGEKP
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SEQIDNO:18 YKC--TVCGKSFSXXXXXXXHKRL-HTGEKP
SEQIDNO:19 FSC--NYCQRKFGXXXXXXXHVRI-HQNKK

The Office has not provided any evidence that any one of Barbas's 6 sequences (fingers 1-3 of Zif268 or fingers 1-3 of TFIIIA) is identical to a ZFP produced from a plant ZFP, as recited in the claims. Indeed, in light of the sequence alignments presented above, the chance that a ZFP that is not produced from Zif268 or TFIIIA (as are the ZFPs recited in the claims) would be identical to one of Barbas's proteins is astronomically small.

Thus, contrary to the Examiner's assertions, Applicants have shown that the process by which modified plant ZFPs are produced (namely modifying naturally occurring plant zinc finger proteins) will necessarily result in a ZFP having a different sequence than any of Barbas's proteins (which consist of Zif268 or TFIIIA backbones with modified recognition helices). See Final Office Action, pages 7-8). Applicants have also shown that the differences imparted by the claimed process are found in regions outside the recognition helix. *Id.* Finally, Applicants have established that the differences imparted by the process are maintained in the ZFPs used in the claimed methods because the sequence are necessarily different, and that these different sequences (outside the recognition helix region) are incorporated into the claimed ZFPs.

Thus, Applicants have demonstrated that there are clear structural differences between the proteins used in the claimed methods and those disclosed by Barbas. Moreover, there is nothing in the record (nor in the art) to support the assertion that Barbas discloses or suggests the modified plant ZFPs recited in the claims.

Therefore, the ZFPs used in the claimed methods are structurally distinguishable from those disclosed or suggested by Barbas and withdrawal of the rejections based on Barbas is in order.

35 U.S.C. § 103

Claims 14 and 33 were rejected under 35 U.S.C. § 103 as allegedly obvious over Barbas in view of U.S. Patent No. 6,706,470 (hereinafter "Choo"). (Office Action, pages 13-14).

Claims 14 and 33 depend from claims 1 and 21 respectively. For the reasons noted above, Barbas does not in any way teach or suggest altering Zif268 or TFIIIA outside of

particular residues in the 7 amino acid recognition region. In fact, Barbas teaches away from such alterations inasmuch as residues outside the recognition helix region are purposefully left unchanged, compared to wild-type Zif268 and TFIIIA.

Accordingly, claims 14 and 33 are not obvious over Barbas, alone or in combination with Choo, and the rejection may be withdrawn.

CONCLUSION

Applicants submit that the claims are in condition for allowance and request early notification to that effect. If the Examiner has any further issues or wishes to discuss any of the foregoing, they are invited to contact Applicants' undersigned attorney at the telephone number listed below.

Respectfully submitted,

Date: August 15, 2006

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